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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,087	11/20/2001	Stephen G. Sligar	87-00	1280

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,087	SLIGAR ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,41-49 and 52-59* is/are pending in the application.

4a) Of the above claim(s) *44-49 and 52-58* is/are withdrawn from consideration.

5)☒ Claim(s) *59* is/are allowed.

6)☒ Claim(s) *37 and 41* is/are rejected.

7)☒ Claim(s) *42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Request filed on 06/17/2005 for Continued Examination (RCE) under 37 CFR 1.114 of Application 09/990,087 is granted. An action on the RCE follows.

Applicants' amendment filed on 06/17/2005 has been entered. Claim 37 has been amended. Claims 37, 41-49 and 52-59 are pending. Claims 37, 41-43, and 59 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

The information disclosure statement filed on 06/17/2005 has been considered by the examiner.

Claim Rejections under 35 USC § 103 (a)

The rejection of claims 37 and 41 under 35 U.S.C. 103(a) as being unpatentable over Bayburt et al. (*Journal of Structural Biology* 123:37-44, 1998) in view of Barnes et al. (Neuropharmacology 38:1083-1152, 1999), as set forth in Paper No. 12272004 (mailed on 12/30/2004), is maintained. For clarity, the rejection is reproduced below.

(i). Claims 37 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bayburt et al. (*Journal of Structural Biology* 123:37-44, 1998) in view of Barnes et al. (Neuropharmacology 38:1083-1152, 1999).

Bayburt et al. teach reconstitution and imaging of an integral membrane protein, NADPH-cytochrome P450 reductase in a nanometer-size phospholipid bilayer. This nanobilayer consists of an approximately 10-nm-diameter circular (discoidal) phospholipid domain stabilized by apolipoprotein A1, an amphipathic membrane scaffold protein (see, e.g., Abstract), which forms α-helices (top of right column of page 37). The apolipoprotein A1 has eight 22-mer and two 11-mer tandem amino acid sequence repeats, each with the periodicity of an amphipathic α- helix.

Bayburt et al. fail to teach a nanoscale particle comprising a G-protein coupled receptor, such as a 5-hydroxytryptamine receptor.

Barnes et al. teach the structures and biological functions of 5-hydroxytryptamine receptors. Barnes et al. teach a high level of interest in the actions of 5-hydroxytryptamine and that pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutic potential (see, e.g., Abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute a 5-hydroxytryptamine receptor of Barnes et al.

in the nanometer-size phospholipid bilayer taught by Bayburt et al. with a reasonable expectation of success. One would have been motivated to do so because (i) the nanometer-size phospholipid bilayer provides a novel approach for the study of mechanical and functional properties of single-membrane proteins in a bilayer environment, which represents a physiologically relevant condition, as taught by Bayburt et al (see, e.g., Abstract; 2nd paragraph of left column of page 38; last paragraph of left column of page 44); and (ii) pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutic potential (see, e.g., Abstract), as taught by Barnes et al.

(ii). Response to Applicants' Argument

Beginning at page 6 of Applicants' response filed on 06/17/2005, Applicants argue that the present claims encompass artificial membrane scaffold proteins neither taught nor suggested by the cited Bayburt reference. Applicants argue that the Bayburt paper describes particles prepared using cytochrome reductase and naturally occurring human apolipoprotein A-1. Applicants submit that the specification gives numerous non-limiting examples of the kinds of differences in structure between natural apo A-1 and thus the artificial membrane scaffold proteins of the present invention are clearly distinguished in structure from naturally occurring human proteins.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the term "artificial" does not limit the scope of the claimed invention and does

not distinguish the scaffold protein recited in the instant claims from those taught in the art because a membrane scaffold protein, e.g., apo A-I protein, can be made by DNA recombinant technology and such an artificial scaffold protein can have the same sequence as that of a membrane scaffold protein isolated from a natural source. The specification does not provide an unambiguous definition for the term "artificial" that clearly excludes those membrane scaffold proteins that have the same structure as that of naturally occurring membrane scaffold proteins.

At the 2nd paragraph of page 7 of Applicants' response filed on 06/17/2005, Applicants argue that the cited Bayburt reference makes no teaching or suggestion that a protein with more than a single segment inserted into a membrane or nanoscale discoid particles should be or could be successfully incorporated into a nanoscale particle, nor does this reference teach or suggest that any membrane scaffold protein structures could be designed for use together with GPCRs in nanoscale discoid particles. Applicants submit that the GPCRs are significantly more complex than cytochrome P450.

Applicants' argument has been fully considered, but is not deemed to be persuasive because it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute a GPCR, such as a 5-hydroxytryptamine receptor in the nanometer-size phospholipid bilayer taught by Bayburt et al. with a reasonable expectation of success. One would have been motivated to do so because

Bayburt et al. clearly demonstrate the success of reconstitution and imaging of an integral membrane protein, NADPH-cytochrome P450 reductase in a nanometer-size phospholipid bilayer and teach that this can be used as a novel approach to study mechanical and functional properties of single-membrane proteins in a bilayer environment, which represents a physiologically relevant condition and because Barnes et al. teach that pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutically potential. Moreover, the demonstration of the success of reconstitution of an active integral membrane protein, NADPH-cytochrome P450 reductase, which is a complex membrane protein enzyme system, in a nanometer-size phospholipid bilayer illustrates the reasonable expectation of success that one of skilled in the art reconstitute other membrane proteins, such as 5-hydroxytryptamine receptor, a GPCR. In a word, it is a logic evolution for one skilled in the art from reconstitution of NADPH-cytochrome P450 reductase with a single segment in a nanometer-size phospholipid bilayer to reconstitution of a GPCR with more than a single segment, such as a 5-hydroxytryptamine receptor in the nanometer-size phospholipid bilayer.

Beginning at the bottom of page 7 of Applicants' response filed on 06/17/2005, Applicants argue that the reference of Barnes et al. makes no suggestion any GPCR could be combined with an artificial membrane scaffold protein in a nanoscale disc-like particle. Applicants submit that Applicants' own disclosure cannot be the source of the motivation to combine elements. Citing case law, Applicants argue that the courts have cautioned against the impermissible use of hindsight in evaluating patentability.

Applicants' argument has been fully considered, but is not deemed to be persuasive because, in combination with the teaching of Bayburt et al. that reconstitution of NADPH-cytochrome P450 reductase with an amphipathic membrane scaffold protein, human apolipoprotein A1, in a nanometer-size phospholipid bilayer can be used for studying mechanical and functional properties of single-membrane proteins in a physiologically relevant condition, the teaching of Barnes et al. provides a motivation to reconstitute a GPCR, such as 5-hydroxytryptamine with the human apolipoprotein A1 in a nanometer-size phospholipid bilayer because there is a high level of interest in the actions of 5-hydroxytryptamine and pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutically potential. Regarding Applicants argument about the impermissible use of hindsight, the Examiner notes that it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art *In re Keller,* 642 F.2d 413, 288 USPQ 871 9ccpa 1981).

At the middle of page 8 of Applicants' response filed on 06/17/2005, Applicants argue that neither cited reference makes any suggestion that it would be possible to incorporate a protein with so complex a membrane interaction as a GPCR into a nanoscale particle, that the apolipoprotein A1 primary structure could be modified or that native ligand binding of a GPCR could be or would be maintained in a nanoscale particle such as taught and claimed in the present application. Applicants submit that

there is nothing in the cited references that would provide the requisite reasonable expectation of success in carrying out the invention as claimed.

Applicants' argument has been fully considered, but is not deemed to be persuasive. As noted above, it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute a GPCR, such as a 5-hydroxytryptamine receptor in the nanometer-size phospholipid bilayer taught by Bayburt et al. with a reasonable expectation of success. One would have been motivated to do so because Bayburt et al. clearly demonstrate the success of reconstitution and imaging of NADPH-cytochrome P450 reductase in a nanometer-size phospholipid bilayer and teach that this can be used as a novel approach to study mechanical and functional properties of single-membrane proteins in a bilayer environment, which represents a physiologically relevant condition and because Barnes et al. teach that pharmacological manipulation of the central 5-hydroxytryptamine system has therapeutically potential. The demonstration of the success of reconstitution of an active integral membrane protein, NADPH-cytochrome P450 reductase, which is a complex membrane protein enzyme system, in a nanometer-size phospholipid bilayer illustrates the reasonable expectation of success that one of skilled in the art reconstitute other membrane proteins, such as 5-hydroxytryptamine receptor, a GPCR. Also as noted above, while claim 37 recites a nanoscale particle comprising an artificial membrane scaffold protein, the term "artificial" does not limit the scope of the claimed invention and does not distinguish the scaffold protein recited in the instant claims from those taught in the art

because a membrane scaffold protein, e.g., apo A-I protein, can be made by DNA recombinant technology and such an artificial scaffold protein can have the same sequence as that of a membrane scaffold protein isolated from a natural source.

For the reasons set forth above, the rejection of claims 37 and 41 under 35 U.S.C. 103(a) as being unpatentable over Bayburt et al. in view of Barnes et al. is maintained.

Claim Objection

Claims 42 and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claim 59 is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Anthony Caputa, can be reached on (571) 272-0829. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Primary Examiner
August 29, 2005